PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

B8

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 277/42, 277/54, A61K 31/425

A1

(11) International Publication Number: WO 99/62892

(43) International Publication Date: 9 December 1999 (09.12.99)

(21) International Application Number: PCT/EP99/03682

(22) International Filing Date: 27 May 1999 (27.05.99)

(30) Priority Data:
198 24 175.5 29 May 1998 (29.05.98) DE

(71) Applicant *(for all designated States except AT US)*: NOVARTIS AG [CH/CH]; Schwarzwaldallee 215, CH–4058 Basel (CH).

(71) Applicant *(for AT only)*: NOVARTIS–ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H. [AT/AT]; Brunner Strasse 59, A–1230 Vienna (AT).

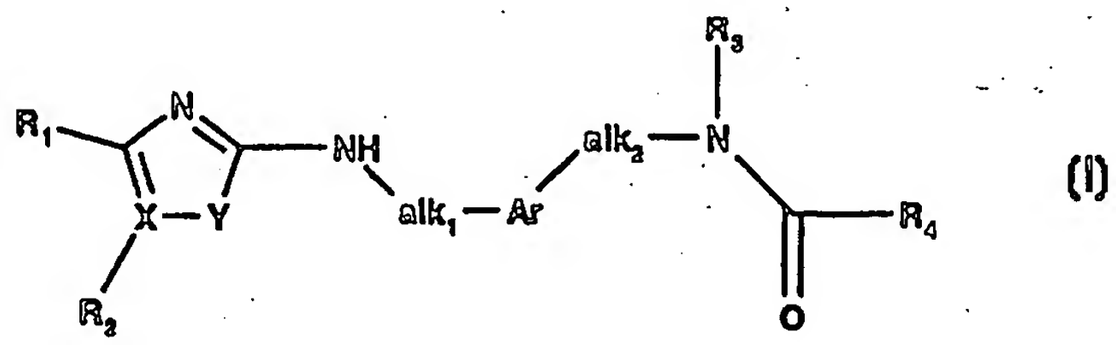
(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: BÜHLMAYER, Peter [CH/CH]; Hangstrasse 18, CH–4144 Arlesheim (CH).

(74) Agent: BECKER, Konrad; Novartis AG, Corporate Intellectual Property, Patent & Trademark Dept., CH–4002 Basel (CH).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: AMINOAZOLE COMPOUNDS



(I)

(57) Abstract

The invention relates to a compound of formula (I), wherein the variables have the meanings indicated, or a salt thereof; methods for their preparation, pharmaceutical compositions, and the use of compounds of formula (I) and salts thereof.

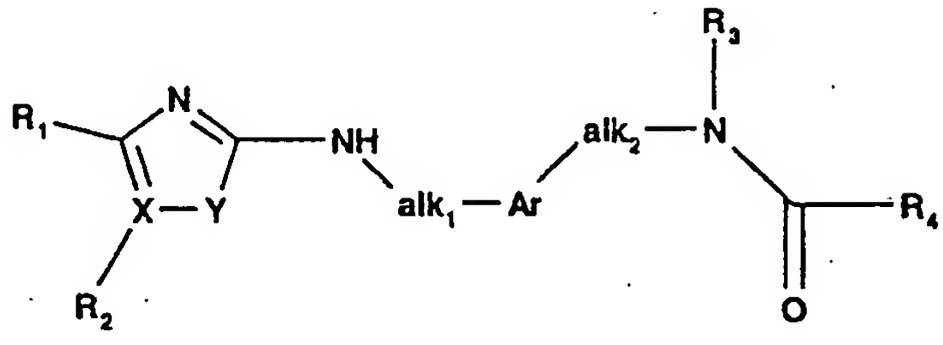
FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania
AM	Armenia
AT	Austria
AU	Australia
AZ	Azerbaijan
BA	Bosnia and Herzegovina
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CU	Cuba
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GH	Ghana
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IL	Israel
IS	Iceland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgyzstan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakstan
LC	Saint Lucia
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LS	Lesotho
LT	Lithuania
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
MK	The former Yugoslav Republic of Macedonia
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TM	Turkmenistan
TR	Turkey
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam
YU	Yugoslavia
ZW	Zimbabwe

Aminoazole Compounds

The invention relates to a compound of formula (I),



(I), wherein

(i) alk_1 and alk_2 are independently a bond or C_1-C_4alkylene;

X is the C atom and Y the S, O or NH atom; or

X is the N atom and Y is the N atom;

Ar is phenylene;

R_1 is hydrogen, C_1-C_7alkyl, C_1-C_7alkoxy-C_1-C_7alkyl, C_3-C_8cycloalkyl-C_1-C_7alkyl, C_1-C_7alkoxy, C_1-C_7alkoxy-C_1-C_7alkoxy, CF_3, halogen, nitro or cyano, or R_1 is phenyl, pyridyl, pyrrolyl, furyl or thienyl;

R_2 has the same meanings as R_1 if X is C, or is hydrogen, C_1-C_7alkyl or C_3-C_8cycloalkyl-C_1-C_7alkyl if X is N;

R_3 and R_4 are independently hydrogen, C_1-C_7alkyl, C_1-C_7alkoxy-C_1-C_7alkyl, C_3-C_8cycloalkyl-C_1-C_7alkyl, halogeno-C_1-C_7alkyl, aminocarbonyl-C_1-C_7-alkyl, wherein the amino group is unsubstituted or is monosubstituted or disubstituted independently by C_1-C_7alkyl or phenyl-C_1-C_7alkyl, or they are phenyl or phenyl-C_1-C_7alkyl; whereas R_3 and R_4 are not simultaneously hydrogen; or

R_3 and R_4 together are C_3-C_4alkylene;

wherein an (hetero)aromatic radical phenylene, phenyl, pyridyl, pyrrolyl, thienyl, furyl is independently unsubstituted or substituted once or several times by a substituent selected from the group comprising C_1-C_7alkyl, C_1-C_7alkoxy-C_1-C_7alkyl, hydroxy, C_1-C_7alkoxy, C_1-C_7alkoxy-C_1-C_7alkoxy, CF_3, halogen, nitro and cyano;

(ii) also to a corresponding compound of formula (I), wherein R_1 is phenyl disubstituted by oxy-C_1-C_2alkylene-oxy, which is furthermore unsubstituted or substituted once or several times by a substituent selected from the group consisting of C_1-C_7alkyl, C_1-C_7alkoxy-C_1-C_7alkyl, hydroxy, C_1-C_7alkoxy, C_1-C_7alkoxy-C_1-C_7alkoxy, CF_3, halogen, nitro and cyano;

(iii) also to a corresponding compound of formula (I), wherein R_3 and R_4 are independently furanyl or pyranyl;
or a salt, especially a pharmaceutically acceptable salt, thereof; methods for their preparation, pharmaceutical compositions, and the use of compounds of formula (I) and salts thereof.

The compounds of formula (I) may be present in the form of salts, in particular pharmaceutically acceptable salts. In each case, acid addition salts may be formed with the basic amino group. Suitable acid components are for example strongly inorganic acids, such as mineral acids, for example halogen halides, e.g. hydrochloric acid, or strongly organic carboxylic acids, for example acetic acid or trifluoroacetic acid, or organic sulfonic acids, e.g. methanesulfonic acid or p-toluenesulfonic acid. In a broader sense, the invention relates also to salts which are not suitable for therapeutic purposes and may be used for example in the isolation or purification of free compounds of formula (I) or pharmaceutically acceptable salts thereof. Only salts that are pharmaceutically acceptable and non-toxic are used therapeutically and those salts are therefore preferred.

If compounds of the invention have at least two optically active carbon atoms, they may be present in the form of stereoisomers, stereoisomeric mixtures, and (essentially) pure diastereomers. Corresponding compounds with an optically active C atom are present in the form of racemates, especially in the form of (essentially) pure enantiomers. Corresponding stereoisomers are likewise a subject of the present invention.

The general terms used hereinbefore and hereinafter have the following meanings, unless defined otherwise.

C_1-C_4alkylene is especially methylene, ethylene, n-propylene, n-butylene, 1,2- or 2,3-propylene or 1,2-, 1,3- or 2,3-butylene. Methylene is preferred.

Phenylene is 1,2- 1,3- or 1,4-phenylene.

C_1-C_7alkyl is for example methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl or a corresponding pentyl, hexyl or heptyl radical. C_1-C_4alkyl, especially methyl, is preferred.

C_1-C_7alkoxy is for example methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy, isobutyloxy, sec-butyloxy, tert-butyloxy or a corresponding pentyloxy, hexyloxy, or heptyloxy radical. C_1-C_4alkoxy is preferred. Methoxy is especially preferred.

C_1-C_7alkoxy-C_1-C_7alkyl is in particular C_1-C_4alkoxy-C_1-C_4alkyl, such as methoxyethyl, 2-ethoxyethyl, 2-n-propyloxyethyl or ethoxymethyl.

C_1-C_7alkoxy-C_1-C_7alkoxy is in particular C_1-C_4alkoxy-C_1-C_4alkoxy, such as methoxyethoxy, 2-ethoxyethoxy, 2-n-propyloxyethoxy or ethoxymethoxy.

Pyridyl is 2-, 3-, or 4-pyridyl.

Pyrrolyl is 2- or 3- pyrroyl, furyl 2- or 3- furyl, thienyl 2- or 3- thienyl.

Halogen is in particular halogen with an atomic number up to and including 35, i.e. fluorine, chlorine or bromine, and in a broader sense includes iodine. Fluorine or chlorine is preferred.

C_3-C_7cycloalkyl-C_1-C_7alkyl is in particular C_3-C_6cycloalkyl-C_1-C_4alkyl, for example cyclopropylmethyl or -ethyl, cyclobutylmethyl or -ethyl, cyclopentylmethyl or -ethyl, or cyclohexylmethyl or -ethyl. Cyclopropylmethyl is especially preferred.

Halogeno-C_1-C_7alkyl is in particular halogeno-C_1-C_4alkyl, for example chloromethyl, trifluoromethyl, 2-trifluoroethyl, 2-chloroethyl or 2,2,2-trifluoroethyl.

Phenyl-C_1-C_7alkyl is in particular phenyl-C_1-C_4alkyl, such as benzyl or 1- or 2-phenethyl.

(Hetero)aromatic radicals, unless otherwise defined, are unsubstituted or substituted once or several times, for example disubstituted or trisubstituted, by a substituent selected from the group comprising C_1-C_4alkyl, C_1-C_4alkoxy, halogen, CF_3, cyano and nitro. Phenyl disubstituted by oxy-C_1-C_2alkylene-oxy is in particular phenyl 1,2-disubstituted by oxy-methylene-oxy.

Obesity is a widespread phenomenon, which is responsible for a wide range of disease symptoms and has a negative influence on health as a whole. In addition, obesity is associated with substantial socioeconomic costs and represents a major financial burden on the healthcare system. To solve this problem, an approach must be found by which obesity and the associated diseases and disorders can be systematically treated. It has been found that eating behaviour can be regulated by modulating the Y5 receptor subtype of neuropeptide Y (NPY).

Extensive pharmacological studies have shown that compounds of formula (I) and pharmaceutically acceptable salts thereof are suitable as antagonists of the neuropeptide Y5 receptor subtype.

The compounds of the present invention and pharmaceutically acceptable salts thereof have been demonstrated to have a marked and selective affinity for the Y5 receptor (demonstrated in Y5-receptor binding studies) and to show anatagonistic properties both in vitro and in vivo. These properties manifest themselves in vitro through their ability to inhibit the NPY-induced elevation of calcium in stably transfected cells which express the Y5 receptor. In vivo, the antagonistic effect manifests itself in the ability to inhibit the feeding induced in conscious rats either by intraventricular administration of NPY or 24-hour food deprivation.

Binding assays

The selective affinity of the compounds (according to the present invention) for the Y5 receptor was demonstrated in a Y5-binding assay using both LM(tk-)-hY5-7 cells, which normally express NPY5 receptor in humans, and HEK-293 cells, which normally express the NPY5 receptor in rats.

The following buffers were used for preparing the membranes and for the binding assay: a) Buffer 1 (homogenization buffer, pH 7.7 at 4 °C) comprises Tris-HCl [FLUKA, Buchs, Switzerland] (20 mM) and ethylenediaminetetraacetic acid (EDTA) [FLUKA, Buchs, Switzerland] (5 mM); b) Buffer 2 (suspension buffer, pH 7.4 at room temperature) comprises N-2-hydroxyethylpiperazin-N'-2-ethanesulfonic acid (HEPES) [Boehringer Mannheim,

Germany] (20 mM), NaCl (10 mM), $CaCl_2$ (1.26 mM), $MgSO_4$ (0.81 mM) and KH_2PO_4 (0.22 mM); c) Buffer 3 (bindung buffer, pH 7.4 at room temperature) comprises HEPES (20 mM), NaCl (10 mM), $CaCl_2$ (1,26 mM), $MgSO_4$ (0.81 mM) and KH_2PO_4 (0.22 mM) and 1 mg/ml bovine serum albumin [FLUKA].

The cells are washed in phosphate-buffered physiological saline and collected with the help of a rubber policeman. The cells are homogenized in ice-cooled hypotonic buffer solution (buffer 1, pH 7.7, at 4°C) using a Polytron homogenizer (3 impulses of 8 seconds) The homogenate is centrifuged for 20 minutes at 32.000 g and 4°C. The sediment is resuspended in the same buffer and centrifuged again. The resulting sediment is suspended in buffer 2. The protein concentration is determined using the Coomassie blue method [Pierce, Socochim, Lausanne, CH]. Bovine serum albumin is used as reference standard. The raw membrane suspension is divided into aliquots, frozen in liquid nitrogen, and stored at -80°C. Before it is used, 0.1% (1 mg/ml) bovine serum albumin is added. ^{125}I-[Pro^{34}]hPYY (60 pM final concentration, Anawa, Wangen, Switzerland], dissolved in buffer 3, is used as radioligand.

All compounds to be tested are dissolved in 10^{-2} M dimethyl sulfoxide (DMSO) and diluted with buffer 3 to 10^{-3} M. Further dilutions are prepared with buffer 3 plus 10% DMSO. The incubations are carried out in Millipore MultiScreen FB filter plates [Millipore, Bedford, USA]. The filter wells aligned to each of the sample wells are pretreated with 2% polyethyleneimine for 30 minutes and rinsed once before use with 300 µl buffer 3. The following substances are pipetted into each sample well. 60 µl buffer 3, 20 µl ^{125}I-[Pro^{34}]hPYY (600 pM), 20 µl of the compound to be tested (or binding buffer plus 10% DMSO for the controls), 100 µl raw membrane suspension (approximately 10 µg protein). Incubation is carried out at room temperature over a period of 2 hours. Non-specific binding is defined as binding which still takes place in the presence of 1 µM [Pro^{34}]hPYY [BACHEM, Bubendorf, Switzerland]. The incubation is terminated by rapid filtration and fourfold washing with 300 µl phosphate-buffered saline. The filters are removed from the wells of the plate, placed in plastic tubes, and measured for radioactivity in a gamma counter [Gammamaster, WALLAC, Finland].

The IC50 values of the compounds (of the present invention) in the human Y5 receptor lie in most cases between about 0.1 nM and about 10 µM. Illustrative of the invention, the following IC_{50} values have been determined in the human Y_5 receptor assay:

Compound of Example	IC_{50} [µM]
19	0.016
30	0.0066
32	0.0042

Measurement of calcium increase

To determine the antagonistic properties of the compounds (according to the submitted invention) in vitro stably transfected LM(tk-)-hY5-7 cells were used in which an NPY-induced increase in calcium was measured as follows. The cells are collected in a medium comprising EDTA (0.5 mM) and phosphate-buffered saline (PBS). The cells are then washed in phosphate-buffered saline and incubated for 90 minutes at room temperature and pH 7.4 with 10 µM FLUO-AM (fluo-3 acetoxymethyl ester, supplemented with Pluronic as suggested by the manufacturer, Molecular Probes Inc., Eugene, Oregon, USA) in a cell culture buffer of the following composition (NaCl 120 mM, $MgCl_2$ 1 mM, KCl 5.4 mM, NaH_4PO_4 0.33 mM, glucose 11 mM, taurine 5 mM, pyruvate 2 mM, glutamine 1.5 mM, HEPES 10 mM, insulin 10 E/l, BSA 0.1 %). After centrifugation, the cells are resuspended in the cell culture buffer in a concentration of 3–4 million cells/ml, to which 200 µM sulfinpyrazone is added.

The calcium increase is measured at room temperature in a Millititer plate with CytoFluor 2350 (Millipore) at wavelengths of 485 nm (excitation) and 530 nm (emission). 180 µl of the cell suspension is incubated for 5 minutes in the presence of various quantities of compound which are dissolved in 2 µl DMSO (three replicates in each case) (or in 2 µl DMSO for the controls). Finally, NPY is added in a final concentration of 100 nM. The concentrations of the compounds which lead to a 50% inhibition of the maximum calcium increase are calculated.

In this cell system, NPY induces a calcium increase at an EC50 of 50 nM. The data were analysed using Microsoft Excel software. The concentrations which led to a 50% inhibition of the initial values in the controls are given as IC50 values. The IC50 values were determined for the compounds of the present invention and the pharmaceutically acceptable salts thereof.

The ability of the compounds and their pharmaceutically acceptable salts to inhibit the NPY-induced rise in intracellular calcium confirms their antagonistic properties. The IC50 values in most cases lie between about 0.1 nM and about 10 µM.

Measurement of NPY-induced feeding in conscious rats

This antagonism of the Y5 receptor subtype is also observed in vivo using conscious rats in which NPY-induced feeding can be inhibited. For these studies, the food intake was measured in sated rats after cerebroventricular (i.c.v.) adminstration of neuropeptide Y [BACHEM, Feinchemikalien, Bubendorf, Switzerland] both with and without additional administration of compounds (as described in the present invention). All studies were carried out using male Sprague-Dawley rats weighing between 180 and 220 g. The animals were kept in individual Makrolon cages with a photoperiod comprising 11 hours of light and 13 hours of dark (the latter from 18.00) under controlled temperatures (21–23°C). Water and feed (NAFAG lab feed pellets) [NAFAG, Gossau, Switzerland] were available ad libitum. A stainless-steel guiding cannula was implanted in the direction of the right cerebral ventricle in each rat under Vetanarcol anaesthesia (50 mg/kg, intraperitoneal) [VETERINARIA AB, Zürich, Switzerland]. The stereotactic coordinates were as follows: -0.8 mm anterior and +1.3 mm lateral to the bregma, the elevation being –2.0 mm below the interaural line. The guiding cannula was placed on the dura. The injection cannulas jutted out from the guiding cannulas –3.8 mm in a ventral direction (in relation to the cranial surface). The animals were allowed a postoperative recovery phase of at least five days before they were used for the studies.

The fit of the cannulas was checked postoperatively two days before the actual experiments by evaluating the feeding behaviour of all rats following a cerebroventricular (i.c.v.) injection of 300 pmol NPY. For the measurements of NPY-induced feeding, only rats were used which consumed at least 2 g of feed within 2 hours of NPY injection. The injections were

carried out in the morning two afters after the start of the light phase. The peptides were administered in 5–10 µl artificial cerebrospinal fluid (ACSF) [FLUKA, Buchs, Switzerland]. ACSF comprises NaCl 124mM, KCl 3.75mM, $CaCl_2$ 2.5mM, $MgSO_4$ 2.0mM, KH_4PO_4 0.22mM, $NaHCO_3$ 26mM and glucose 10mM. NPY (300 pmol) was given by cerebroventricular injection 10 to 60 minutes after administration of the compounds or the respective vehicle DMSO/water (10% V/V), Cremophor/water (20% V/V) [SIGMA, Buchs, Switzerland] or Tween 80/water (10% V/V) [FLUKA, Buchs, Switzerland].

The food intake was determined by reference to a previously weighed amount of feed pellets placed in the cages at the time of injection with NPY. At each of the times indicated in the figures, the pellets were removed from the cages and replaced by new, previously weighed pellets.

All results are given as mean values ± SEM. Statistical analysis was carried out by analysis of variance. Post hoc comparisons were carried out using the Student-Newman-Keuls test. Statistical significance was assumed at $p < 0.05$.

The compounds of the present invention led to an inhibition of NPY-induced feeding in rats following oral, intraperitoneal, subcutaneous, intravenous and transdermal administration, mostly at doses between about 0.01 and about 100 mg/kg.

<u>Measurement of feeding in rats after 24 hours' food deprivation</u>

On the basis of the observation that food deprivation leads to an increase in the concentration of NPY in the hypothalamus, it is assumed that NPY is responsible for the feeding induced by hunger. The compounds (of the submitted invention) were therefore also studied in rats after 24 hours' food deprivation. These studies were carried out using male Sprague-Dawley rats weighing between 180 and 250g. The animals were kept for the duration of the study in separate cages and, except for the 24-hour period of fasting, received food and mains water ad libitum. The animals were kept at 22 ± 2°C with controlled air humidity and a photoperiod comprising 12 hours of light (from 6.00 to 18.00) and 12 hours of dark. After the rats had been admitted to their cages, they were allowed two weeks to become accustomed to their new environment and to the powdered feed or feed pellets [NAFAG, Gossau, Switzerland] (acclimatization phase). At the end of this

phase, the animals were given no food for a period of 24 hours (starting at 8.00 in the morning) At the end of this fasting phase, the compounds of the present invention or an equivalent volume of the respective vehicle DMSO/water (10%, V/V), Cremophor/water (20%, V/V) or Tween 80/water (10%, V/V) were given to the animals by intraperitoneal, intravenous or oral adminstration. Ten to 60 minutes later, the animals were given food again. During the 24 hours that followed, feeding was measured at various times. The inhibition of feeding by the compounds of the present invention was expressed as a percentage of the food intake of the control animals treated with the vehicle.

In this model of rats deprived of food, the compounds of the present invention led to an inhibition of feeding after oral, intraperitoneal, subcutaneous or intravenous administration; the ED50 was between 0.01 and about 100 mg/kg. Illustrative of the invention, the following inhibition values have been determined in this model of food-deprived rats:

Compound of Example	Inhibition of feeding after oral administration [%]: after (i) 1 hour - (ii) 2 hours
1	(i) 51 - (ii) 40
19	(i) 39 - (ii) 40

Measurement of food intake in obese Zucker rats

The anti-obesity efficacy of the compounds of the present invention has also been demonstrated in obese Zucker rats, a known animal model for obesity. The studies were carried out using male, obese Zucker rats (fa/fa) [HARLAN CPB, Austerlitz, NL] weighing between 480 and 500 g. The animals were kept for the duration of the study in separate metabolic cages and received feed in powder form and mains water ad libitum. They were kept in a room with a photoperiod comprising 12 hours of light and 12 hours of dark (the latter from 8.00 to 20.00) a temperature of 24°C, and controlled air humidity. After they had been admitted to their metabolic cages, the rats were allowed six days to become accustomed to their new environment and to the powdered feed (acclimatization phase). At the end of this phase, the food consumption during the periods of light and dark was measured. After a three-day control phase, the animals were treated with the compounds

of the present invention or the DMSO/water (10% V/V), Cremophor/water (20% V/V) [SIGMA, Buchs, Switzerland] or Tween 80/water (10% V/V) [FLUKA, Buchs, Switzerland].

The compounds of the present invention led to an inhibition of feeding in obese Zucker rats following oral, intraperitoneal, subcutaneous, or intravenous administration, mostly at doses between about 0.01 and about 100 mg/kg.

Measurement of food intake in obese mice

The anti-obesity efficacy of the compounds of the present invention has also been demonstrated in genetically obese mice. The studies were carried out using male and/or female mice with an ob/ob mutation (The Jackson Laboratory, Bar Harbor, ME) (C57BL/61-ob) weighing between 30 and 80 g. The mice were kept in Makrolon or metabolic cages and were given feed in powder form and mains water ad libitum. The mice were kept at 24°C and in a photoperiod comprising 12 hours of light (from 8.00 to 20.00) and 12 hours of dark. After they had been admitted to their cages, the mice were allowed six days to become accustomed to their new environment (acclimatization phase). After a three-day control phase, during which the food intake and bodyweight were monitored, the animals were treated with the compounds of the submitted invention or the DMSO/water (10% V/V), Cremophor/water (20% V/V) [SIGMA, Buchs, Switzerland] or Tween 80/water (10% V/V) [FLUKA, Buchs, Switzerland].

The compounds of the present invention led to an inhibition of feeding in the obese ob/ob mice following oral, intraperitoneal, subcutaneous, or intravenous administration, mostly at doses between about 0.01 and about 100 mg/kg.

The animal experiments described above show clearly that the Y5 receptor subtype is the primary mediator of NPY-induced feeding and that appropriate antagonists can be used to treat obesity and related disorders [Nature, Vol. 382, 168 - 171 (1996)].

The compounds of the present invention can inhibit not only feeding induced either by cerebroventricular administration of NPY or by food deprivation but also spontaneous feeding in obese Zucker rats and ob/ob mice. The compounds (of the submitted invention) thus antagonize the binding of neuropeptide Y (NPY) to the Y5 receptor subtype (NPY

antagonism) and could be used in particular for the treatment and prevention of disorders or diseases which are associated with the Y5 receptor, i.e. in which the NPY Y5 receptor is involved. They could preferably be used in the treatment of diseases which are caused by eating disorders, such as obesity, bulimia nervosa, diabetes, dyslipidaemia and hypertension. In addition, they can also be used for the treatment of memory impairment, epileptic seizures, migraine, insomnia and pain, as well as for the treatment of sexual dysfunctions, depression, anxiety states, cerebral haemorrhage, shock, decompensated heart failure, nasal congestion and diarrhoea.

The invention relates to a method of treatment for diseases and disorders associated with the Y5 receptor for NPY, which could be used especially for the prevention and treatment of disorders and diseases involving the Y5 receptor of NPY, preferably for the treatment of diseases caused by eating disorders, such as obesity, bulimia nervosa, diabetes, dyslipidaemia, and hypertension. In addition, they can also be used for the treatment of memory impairment, epileptic seizures, migraine, insomnia and pain, as well as for the treatment of sexual dysfunctions, depression, anxiety states, cerebral haemorrhage, shock, decompensated heart failure, nasal congestion and diarrhoea. The method comprises administering to warm-blooded animals, including humans, that require such treatment a therapeutically effective amount of a compound of formula (I) or of a pharmaceutically acceptable salt thereof.

The invention relates to the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as described hereinbefore and as described also hereinafter for the preparation of a medicament for the prevention and treatment of corresponding diseases or disorders.

The invention relates to a medicament which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, as described hereinbefore and as described also hereinafter for the treatment of corresponding diseases or disorders

The invention relates in particular to a compound of formula (I), wherein alk_1 is a bond or C_1-C_4alkylene and alk_2 is C_1-C_4alkylene; or a salt, especially a pharmaceutically acceptable salt, thereof.

The invention relates in particular to a compound of formula (I), wherein

alk_1 is a bond or C_1-C_4alkylene and alk_2 is C_1-C_4alkylene;

X is the C atom and Y the S, O or NH atom; or

X is the N atom and Y is the N atom;

Ar is phenylene;

R_1 is C_1-C_4alkyl, C_3-C_6cycloalkyl-C_1-C_4alkyl, C_1-C_4alkoxy, CF_3, halogen, nitro or cyano, or R_1 is phenyl, pyridyl, pyrrolyl, furyl or thienyl;

R_2, has the same meanings as R_1 if X is C, or is hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl-C_1-C_4alkyl if X is N;

R_3 is hydrogen, C_1-C_4alkyl, C_1-C_4alkoxy-C_1-C_4alkyl, C_3-C_6cycloalkyl-C_1-C_4alkyl, halogeno-C_1-C_4alkyl, aminocarbonyl-C_1-C_4alkyl, wherein the amino group is unsubstituted or is monosubstituted or disubstituted by C_1-C_7alkyl or phenyl-C_1-C_7alkyl independently of one another, or it is phenyl-C_1-C_7alkyl;

R_4 is hydrogen or C_1-C_4alkyl; whereas R_3 and R_4 are not simultaneously hydrogen; or

R_3 and R_4 together are C_3-C_4alkylene;

wherein an (hetero)aromatic radical phenylene, phenyl, pyridyl, pyrrolyl, thienyl, furyl is independently unsubstituted or substituted once or several times by a substituent selected from the group consisting of C_1-C_4alkyl, C_1-C_4alkoxy-C_1-C_4alkyl, hydroxy, C_1-C_4alkoxy, C_1-C_4alkoxy-C_1-C_4alkoxy, CF_3, halogen, nitro and cyano;

or a salt, especially a pharmaceutically acceptable salt, thereof.

The invention relates in particular to a compound of formula (I), wherein

alk_1 is a bond or C_1-C_4alkylene and alk_2 is C_1-C_4alkylene;

X is the C atom and Y the S, O or NH atom; or

X is the N atom and Y is the N atom;

Ar is phenylene;

R_1 is phenyl or pyridyl;

R_2, has the same meanings as R_1 if X is C, or is hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl-C_1-C_4alkyl if X is N;

R_3 is C_1-C_4alkyl, C_1-C_4alkoxy-C_1-C_4alkyl, halogeno-C_1-C_4alkyl, aminocarbonyl-C_1-C_4alkyl, wherein the amino group is unsubstituted or is monosubstituted or disubstituted by C_1-C_4alkyl or phenyl-C_1-C_4alkyl independently of one another, or it is phenyl-C_1-C_4alkyl;

R_4 is hydrogen or C_1-C_4alkyl; or
wherein an (hetero)aromatic radical phenylene, phenyl or pyridyl is independently unsubstituted or substituted once or several times by a substituent selected from the group consisting of C_1-C_4alkyl, C_1-C_4alkoxy, halogen, CF_3, cyano and nitro.
or a salt, especially a pharmaceutically acceptable salt, thereof.

The invention alternatively relates in particular to a compound of formula (I), wherein X is C; Y is S; or a salt, especially a pharmaceutically acceptable salt, thereof.

The invention relates in particular to a compound of formula (I), wherein
wherein alk_1 is a bond;
alk_2 is C_1-C_2alkylene;
X is the C atom and Y is S;
Ar is phenylene, especially 1,4-phenylene;
R_1 is phenyl, phenyl disubstituted by oxy-methylene-oxy, pyridyl or thienyl;
R_2 is hydrogen, C_1-C_4alkyl, C_1-C_4alkoxy or phenyl;
R_3 is C_1-C_4alkyl, C_1-C_4alkoxy-C_1-C_4alkyl, C_3-C_6cycloalkyl-C_1-C_4alkyl, halogeno-C_1-C_4alkyl, aminocarbonyl-C_1-C_4alkyl, wherein the amino group is unsubstituted or independently monosubstituted or disubstituted by C_1-C_4alkyl, or it is furanyl-C_1-C_4alkyl;
R_4 is hydrogen;
wherein an (hetero)aromatic radical phenylene, phenyl, phenyl disubstituted by oxy-methylene-oxy, pyridyl, thienyl is independently unsubstituted or substituted once or several times by a substituent selected from the group consisting of C_1-C_4alkyl, C_1-C_4alkoxy-C_1-C_4alkyl, hydroxy, C_1-C_4alkoxy, C_1-C_4alkoxy-C_1-C_4alkoxy, CF_3, halogen, nitro and cyano;
or a pharmaceutically acceptable salt thereof.

The invention alternatively relates in particular to a compound of formula (I), wherein
wherein alk_1 is a bond;
alk_2 is C_1-C_2alkylene, such as methylene;
X is the C atom and Y is S;
Ar is 1,4-phenylene;
R_1 is phenyl, phenyl substituted by halogen, typically fluorine, or phenyl disubstituted by oxy-methylene-oxy;

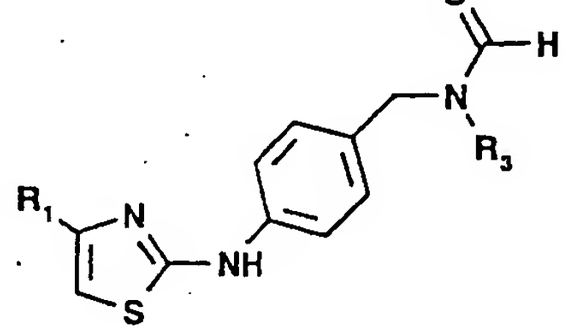
R_2 is hydrogen;

R_3 is C_1-C_4alkyl, such as isopropyl, C_1-C_4alkoxy-C_1-C_4alkyl, such as 2-methoxyethoxy, C_3-C_6-cycloalkyl-C_1-C_4alkyl, such as cyclopropylmethyl, or halogeno-C_1-C_4alkyl, such as 2-fluoroethyl or 2,2,2trifluoroethyl;

R_4 is hydrogen;

or a pharmaceutically acceptable salt thereof.

The invention relates in particular to a compound of formula (I a)



(I a),

wherein

R_1 is phenyl, which is unsubstituted or substituted once or several times by a substituent selected from C_1-C_4alkyl and halogen;

R_3 is C_1-C_4alkyl, C_1-C_4alkoxy-C_1-C_4-alkyl, halogeno-C_1-C_4alkyl or C_1-C_4alkyl, which is substituted by C_1-C_4alkylaminocarbonyl; or a pharmaceutically acceptable salt thereof.

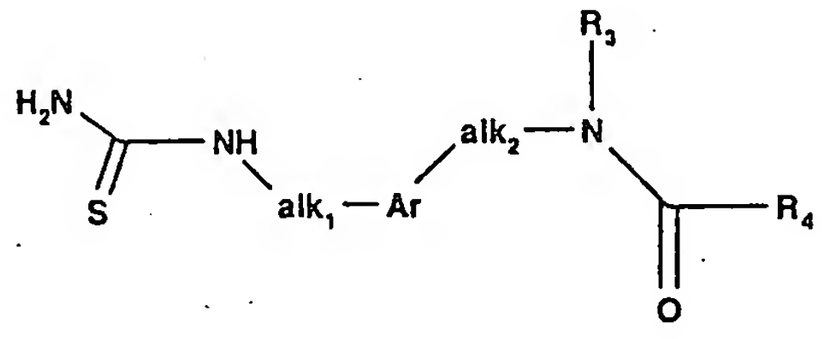
The invention relates in particular to a compound of formula (I a), wherein R_1 is phenyl, which is unsubstituted or mono- or polysubstituted by C_1-C_4alkyl or halogen; R_3 is C_1-C_4-alkyl; or a pharmaceutically acceptable salt thereof.

The invention relates in particular to a compound of formula (I a), wherein R_1 is phenyl or fluorophenyl, such as 3-fluorophenyl; and R_3 is C_1-C_3alkyl, such as methyl, ethyl or isopropyl; or a pharmaceutically acceptable salt thereof.

The invention alternatively relates to a compound of formula (I a), wherein
R_1 is fluorophenyl, such as 3-fluorophenyl; and R_3 is C_3-C_6cycloalkyl-C_1-C_3alkyl,such as cyclopropylmethyl; or a pharmaceutically acceptable salt thereof.

The compounds of the present invention may be manufactured e.g. in a manner known per se.

The invention furthermore relates to the preparation of compounds of the invention. A method for preparing a compound of formula (I), wherein X is C and Y is S, comprising for example the reaction of a compound of formula (II a)



(II a),

with a compound of formula R_1-CH(R_2)-CO-Hal (II b), wherein Hal is halogen.

The reactions described hereinbefore and hereinafter are carried out in a known manner, e.g. in the absence or usually in the presence of a suitable solvent or diluent or a mixture thereof, proceeding as required under conditions of cooling, of ambient temperature, or of heating, e.g. in a temperature range of about -80°C to the boiling temperature of the reaction medium, preferably about -10° to about +200°C, and where appropriate in a closed vessel, under pressure, in an inert gas atmosphere, and/or under non-aqueous conditions.

Halogen Hal is preferably bromine, furthermore chlorine and iodine.

The reaction is carried out preferably in the presence of an organic base. A suitable base for such purposes is for example tri-C_1-C_7alkylamine, such as triethylamine, as is a tri-C_1-C_7alkylamine with voluminous radicals, for example ethyldiisopropylamine, or a heterocyclic base, for example pyridine, 4-dimethylaminopyridine or N-methylmorpholine.

The starting material of formula (II a), wherein X is C and Y is S, can for example be prepared by starting from a compound of formula O_2N-alk_1-Ar-alk_2-Hal (II c), wherein Hal is halogen, especially chlorine, bromine or iodine, preferably bromine, and reacting this with an amine of formula R_3-NH_2 (II d). A compound of formula O_2N-alk_1-Ar-alk_2-NH-R_3 (II e) thus obtained is reacted in the next step with a –CO-R_4 acid halogenide or acid anhydride based on the structural element to form a compound of formula O_2N-alk_1-Ar-alk_2-N(R_3)-CO-R_4 (IIf). For the preparation of a compound

of formula (I) wherein R_4 is hydrogen, formylacetic anhydride or trichloroacetic anhydride is used as a formylating agent. In the following reaction step, the nitro group is reduced to the amino group by means of a suitable reducing agent, for example by hydrogenation with hydrogen in the presence of a hydrogenation catalyst, such as palladium on carbon. This amino group is finally treated with an isothiocyanate, such as benzoylisothiocyanate, which results in a corresponding compound of formula (II a).

The starting material of formula (II b) is known or can be prepared in a known manner. For example, a compound of formula (II b) is obtainable by halogenating a compound of formula R_1-CO-CH_2-R_2 (II g), for example by brominating with bromine.

A method for the preparation of a compound of formula (I), wherein X is C, R_2 is hydrogen, and Y is N, comprising for example the S-alkylation of a compound of formula (II a) as the starting material, for example using methyliodide to form the methylthio derivative, followed by reaction with a compound of formula R_1-CO-$CH(R_2)$-NH_2 (II h) or a salt thereof in the presence of one of the bases stated hereinbefore, for example Hünig's base, to form the corresponding imidazole derivative of formula (I).

The starting material of formula (II h) is known or can be prepared in a known manner.

The invention is illustrated in particular by the following examples and relates also to the compounds said in the examples to be new and to the use of said compounds and to methods for the preparation thereof.

Salts of compounds of formula (I) may be prepared in a known manner. Acid addition salts of compounds of formula (I), for example, are obtainable by treatment with an acid or a suitable ion exchange reagent. Acid addition salts can be converted to free compounds in the usual manner, for example by treatment with a suitable basic agent.

Acid addition salts obtained can be converted in known manner to other salts, for example by treating another acid with a suitable metal salt, such as a sodium, barium, or silver salt, in a suitable solvent, in which a resulting inorganic salt is insoluble and thus eliminated from the reaction equilibrium.

The compounds of formula I, including their salts, are also obtainable in the form of hydrates, or may include the solvent used for crystallization (solvates).

Because the new compounds in free form and in the form of their salts are closely related, the terms free compounds and their salts refer also where appropriate within the meaning and the purpose of this invention to the corresponding salts and free compounds.

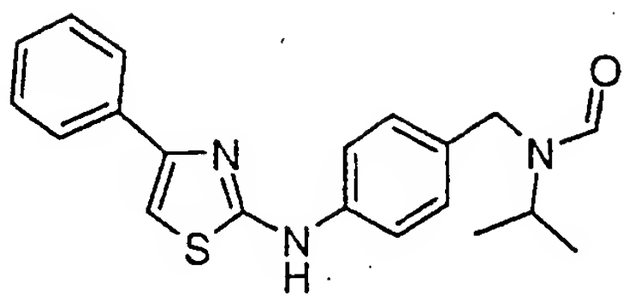
Diastereomeric and racemate mixtures obtained can be separated in known manner, on the basis of the physicochemical differences of the components, into the pure diastereomers and enantiomers, for example by chromatography and/or fractionated crystallization.

The new compounds of formula (I) may be present for example in the form of pharmaceutical preparations which comprise a therapeutically effective amount of active substance, if necessary together with inorganic or organic, solid or liquid, pharmaceutically acceptable carriers, and which are suitable for enteral, for example oral or parenteral, administration. The present pharmaceutical preparations which, if so desired, may contain further pharmacologically active substances are prepared in a manner known per se, for example by means of conventional mixing, granulating, coating, dissolving or lyophilizing processes, and contain from about 0.1% to 100%, especially from about 1% to about 50%, of the lyophilizates to about 100% of the active substance.

The invention relates likewise to the use of compounds of formula (I), preferably for the preparation of pharmaceutical compositions. The dosage may depend on various factors, such as the route of administration, species, age and/or condition of the individual. The daily doses to be administered lie between about 0.25 and about 10 mg/kg in the case of oral adminstration and preferably between about 20 mg and about 500 mg for warm-blooded animals with a bodyweight of about 70 kg.

The following Examples serve to illustrate the invention; temperatures are indicated in degrees centigrade.

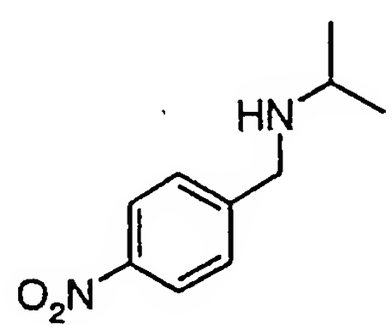
Example 1: N-Isopropyl-N-[4-(4-phenylthiazol-2-ylamino)benzyl]formamide



0.38 g N-Isopropyl-N-(4-thiocarbamoylaminobenzyl)formamide is heated to boiling in 0.21 ml triethylamine and 5 ml ethanol and mixed with 0.3 g phenacylbromide. The mixture is kept under reflux for 20 minutes, then cooled down, taken up in dichloromethane and washed with water. The organic phase is dried over sodium sulfate, evaporated, taken up in acetonitrile and mixed with 1.1 equivalent of hydrochloric acid in ethanol. N-Isopropyl-N-[4-(4-phenylthiazol-2-ylamino)benzyl]formamide is obtained as white crystals. Melting point 173°C.

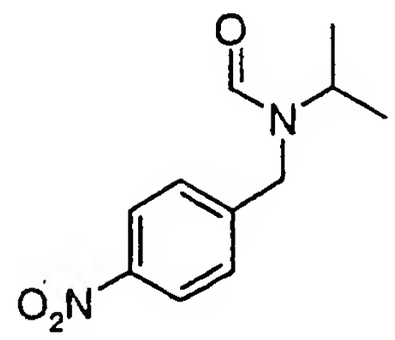
The starting material can be prepared for example as follows:

(a) Isopropyl-(4-nitrobenzyl)amine hydrochloride (CAS Reg. No. 111961-43-4, Beilstein III, Vol. 12, page 2365)



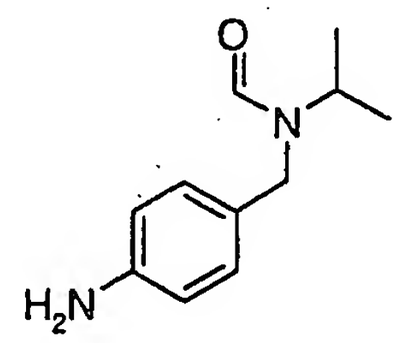
A solution of 5 g p-nitrobenzylbromide in 20 ml dichloromethane is added drop by drop at room temperature to 7 ml isopropylamine in 50 ml toluene. The mixture is stirred at room temperature for 4 hours. The reaction mixture is taken up in ethyl acetate, washed with water and dried over sodium sulfate. The oily residue is dissolved in isopropanol and 5-6 normal hydrochloric acid solution in isopropanol is added. N-Isopropyl-(4-nitrobenzyl)amine hydrochloride is obtained as white crystals. ^{1}H-NMR ($DMSOd_6$): 9.55 ppm (2H, s, wide), 8.3 (2H, d), 7.9 (2H, d), 4.3 (2H, benzyl), 3.3 (1H, m), 1.3 (6H, d).

(b) N-Isopropyl-N-(4-nitrobenzyl)formamide



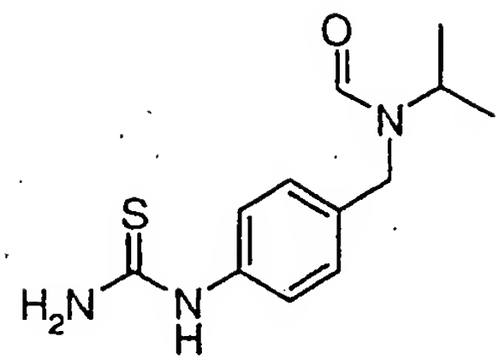
A vessel is prepared with 250 mg isopropyl-(4-nitrobenzyl)amine hydrochloride, 10 ml dichloromethane and 0.754 ml diisopropylethylamine. A solution of 191 mg formylacetic anhydride (mixed anhydride from acetic acid and formic acid, Beilstein E II, Vol. 2, p. 170, H, Vol. 2, p. 165,E IV, Vol. 2, p. 386,E III, Vol. 2, p. 370, CAS Reg.No. 2258-42-6) in 10 ml dichloromethane is added drop by drop over a period of 1 hour. The mixture is stirred at room temperature for 5 hours, extracted with water, dried (sodium sulfate) and evaporated. The residue is dissolved in ethyl acetate and mixed with some ether (turbidity). After standing at room temperature overnight, N-isopropyl-N-(4-nitrobenzyl)formamide precipitates out as a brownish crystallizate. Drying under a high vacuum at 60°C yields the product with a melting point of 136 °C. Rotamers are observed in ^{1}H-NMR ($DMSOd_6$).

(c) N-(4-Aminobenzyl)-N-isopropylformamide



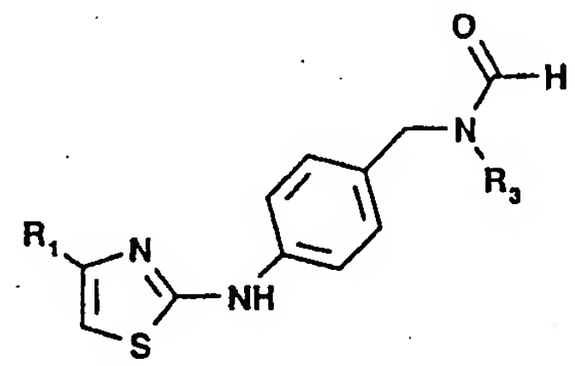
1.37 g N-Isopropyl-N-(4-nitrobenzyl)formamide in 30 ml tetrahydrofuran is hydrogenated in the presence of 0.15 g palladium carbon (10%) at room temperature under normal pressure until saturation. After filtration from the catalyst, the solution was concentrated by evaporation. ^{1}H-NMR ($DMSOd_6$), 2 rotamers in each case: 8.28 and 8.15 ppm (1H, 2s), 6.9 (2H, 2d), 6.5 (2H, 2d), 5.0 (2H, wide), 4.23 und 4.2 (2H, 2s), 4.1 and 3.7 (1H, 2m), 1.1 and 1.0 (6H, 2d). The raw product thus obtained, N-(4-aminobenzyl)-N-isopropylformamide, is used in this form in the next step.

(d) N-Isopropyl-N-(4-thiocarbamoylaminobenzyl)formamide

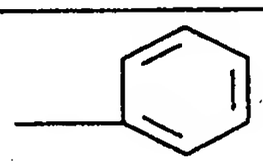
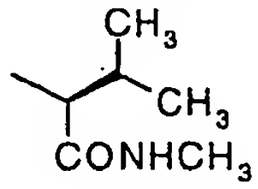
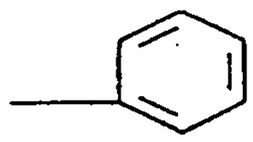
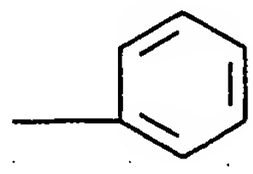


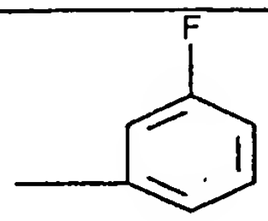
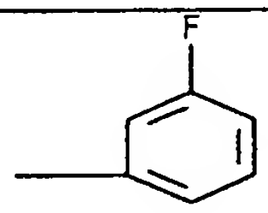
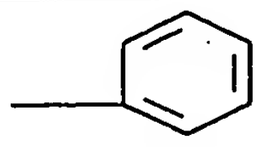
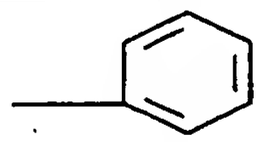
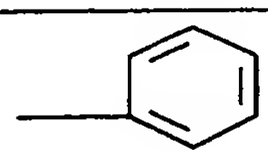
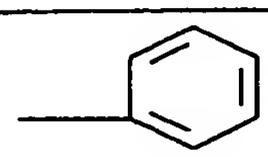
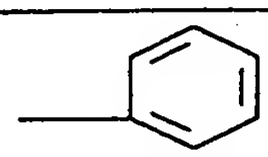
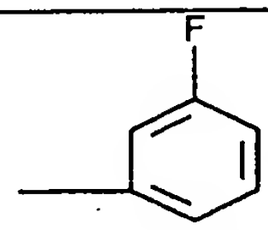
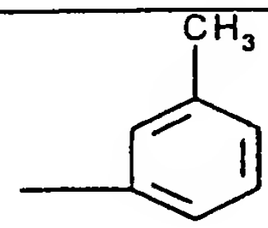
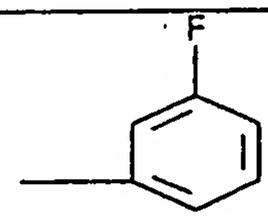
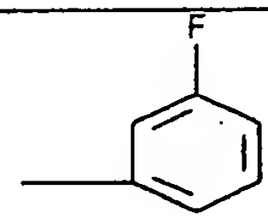
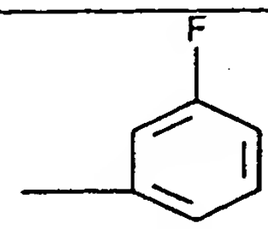
5.4 g N-(4-Aminobenzyl)-N-isopropylformamide in 30 ml tetrahydrofuran is mixed with 2.7 ml benzoylisothiacyanate. The mixture is stirred for 2 hours at room temperature and then concentrated by evaporation in a vacuum. 150 ml methanol and a solution of 2.8 g potassium carbonate in 50 ml water are added and the mixture stirred for 4 hours at room temperature (until dissolved). The reaction mixture is concentrated by evaporation and the remaining aqueous phase is extracted with dichloromethane and dried over sodium sulfate. After evaporation, crystallization from ether is carried out and N-isopropyl-N-(4-thiocarbamoylaminobenzyl)formamide obtained as white crystals. Rf value 0.1 (petroleum ether / ethyl acetate 1:1).

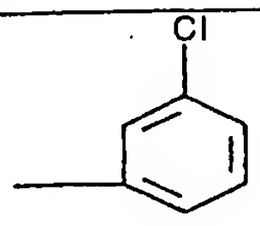
The following compounds of formula (I a) can be prepared in analogous manner, for example as described in Example 1:



(I a)

Example	R_1	R_3	m.p. [°C]
2 *)			90
3		CH_3	136
4 *)		CH_3	144

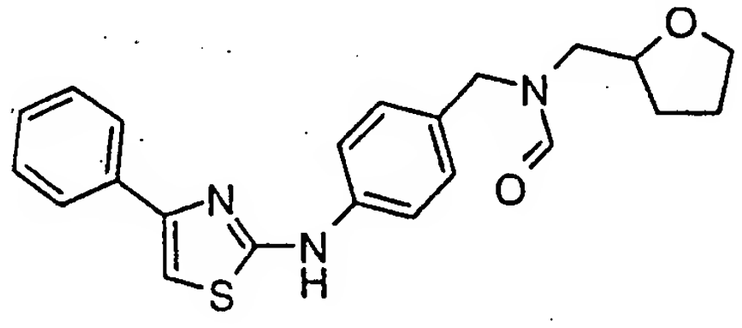
5 *)		C_2H_5	100
6 *)		i-C_4H_9	110
7 *)		C_2H_5	156
8 *)		i-C_4H_9	135
9 *)		n-C_4H_9	100
10 *)		i-C_3H_7	173
11 *)		2-CH_3O-C_2H_4	110
12 *)		i-C_3H_7	115
13 *)		i-C_3H_7	148
14 *)		-CH_2CF_3	150
15 *)		-CH_2CH_2F	178
16 *)		2-CH_3O-C_2H_4	148

17 *)		2-CH_3O-C_2H_4	168

*) = in the form of hydrochloride.

Example 18:

N-[4-(4-Phenylthiazol-2-ylamino)benzyl]-N-(tetrahydrofuran-2-ylmethyl)formamide

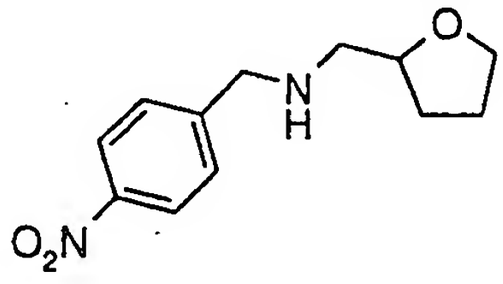


A mixture of 0.78mmol N-(tetrahydrofuran-2-ylmethyl)-N-(4-thioureabenzyl)formamide, 0.78 mmol triethylamine and 0.78 mmol phenacylbromide in 10 ml ethanol is heated to reflux for 20 minutes. After removal of the solvent in the rotary evaporator, thê mixture is taken up in dichloromethane and extracted with water. The organic phase is dried over sodium sulfate and then concentrated by evaporation. The raw product is taken up in 5 ml acetonitrile and converted to the hydrochloride with 1.1 equivalents of an 8.5 N hydrochloric acid solution in ethanol. Crystallization is initiated by addition of diethylether until turbidity is attained. Filtration takes place after 1 hour and drying is carried out at 50° in a high vacuum. N-[4-(4-Phenylthiazol-2-ylamino)benzyl]-N-(tetrahydrofuran-2-ylmethyl)formamide is obtained in the form of slightly greenish crystals. Melting point 144°. Rf value 0.2 (ethyl acetate / petroleum ether 1:1).

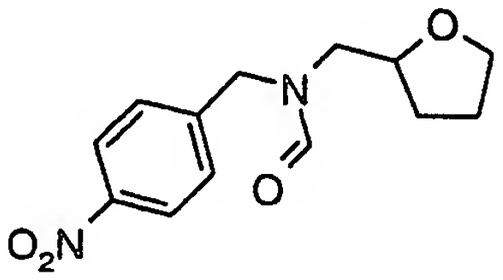
The starting material can be prepared for example as follows:

23 mmol 4-nitrobenzylbromide is added in portions to a solution of 92 mmol tetrahydrofurfurylamine in dichloromethane (temperature rises to about 30°C). The mixture is stirred overnight at room temperature, washed twice with water, dried over sodium sulfate and evaporated and dried under a high vacuum to remove surplus amine. The raw product is converted to the hydrochloride by treatment with 5-6N hydrochloric acid in isopropanol

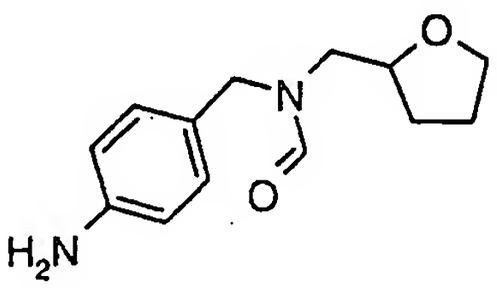
with the addition of some ether. N-4-Nitrobenzyl-N-(tetrahydrofuran-2-ylmethyl)amine hydrochloride is obtained. Rf value 0.1 (ethyl acetate / petroleum ether 1:1).



A solution of 3.6 mmol N-4-nitrobenzyl-N-(tetrahydrofuran-2-ylmethyl)amine (racemate) and 3.96 mmol Hünig's base in 50 ml dichloromethane are cooled to 10°C, and 3.6 mmol trichloroacetic aldehyde is slowly added. The mixture is stirred for 5 hours at 10-15°, the reaction mixture washed with 2N aqueous hydrochloric acid, the organic phase dried over sodium sulfate and evaporated in a vacuum, resulting in N-4-nitrobenzyl-N-(tetrahydrofuran-2-ylmethyl)formamide. Rf value 0.18 (ethyl acetate / petroleum ether 1:1).

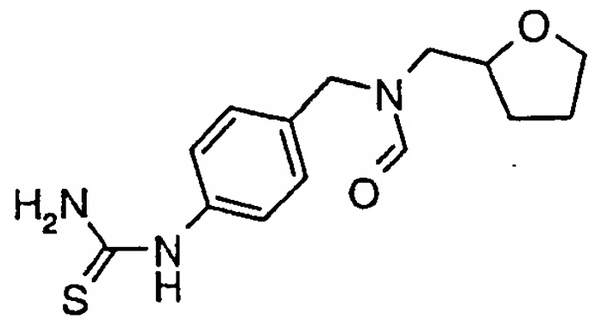


The raw product N-4-nitrobenzyl-N-(tetrahydrofuran-2-ylmethyl)formamide is hydrogenated in the presence of 0.1 g palladium carbon (10%) in 20 ml tetrahydrofuran at room temperature and under normal pressure until saturation. Filtration via Hyflo Supergel (Fluka) yields a colourless solution of N-(4-aminobenzyl)-N-(tetrahydrofuran-2-ylmethyl)formamide. This solution is used directly in the next step without further purification. Rf value 0.12 (ethyl acetate / petroleum ether 1:1).



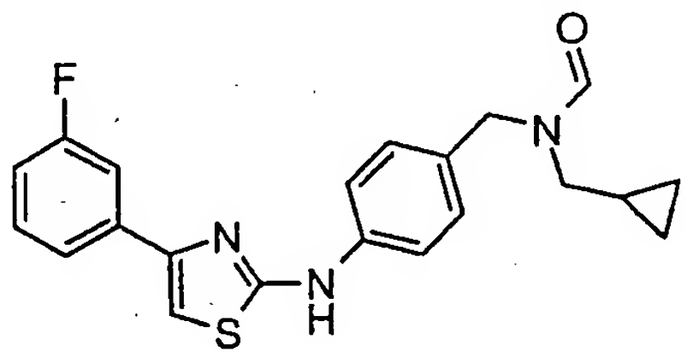
To the solution of N-(4-aminobenzyl)-N-(tetrahydrofuran-2-ylmethyl)formamide obtained above, 3.6 mmol benzoylisothiocyanate is added drop by drop. The solution is stirred for 4 hours and concentrated by evaporation under a vacuum. The resulting intermediate product is readily hydrolysed by treatment in a mixture of methanol and 3.6 mmol potassium carbonate in 50 ml water. After methanol has been evaporated off, the product is extracted

with dichloromethane, dried and crystallized with ether, resulting in N-(tetrahydrofuran-2-ylmethyl)-N-(4-thioureabenzyl)formamide. Rf value 0.02 (ethyl acetate / petroleum ether 1:1).



Example 19:

N-Cyclopropylmethyl-N-{4-[4-(3-fluorophenyl)thiazol-2-ylamino]benzyl}formamide

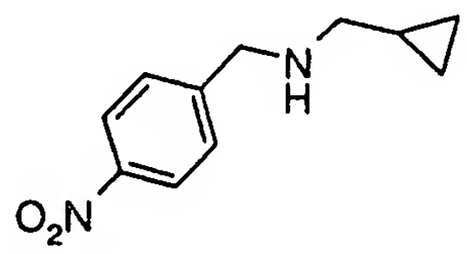


A mixture of 1.14 mmol N-cyclopropylmethyl-N-(4-thioureabenzyl)formamide (96%), 1,14 mmol triethylamine and 1.14 mmol 3-fluorophenacylbromide is heated to reflux for 20 minutes in 10 ml ethanol. After removal of the solvent in the rotary evaporator, the mixture is taken up in dichloromethane and extracted with water. The organic phase is dried over sodium sulfate and then concentrated by evaporation. The raw product is chromatographed on a flash column (silicagel 60, 40-63 micrometer, solvent: petroleum ether / ethyl acetate 1:1 – 2:3). The purified free base is dissolved in acetone and dry hydrochloric acid gas is introduced until pH 1 is achieved. The mixture is cooled to room temperature and treated carefully with ether. After ca. 1 hour the solvent is removed by filtration and the residue is washed with little acetone and then with ether and dried in vacuo at 55 °C for 20 hours. Melting point 154-156 °C. Rf value 0.23 (ethyl acetate / petroleum ether 1:1).

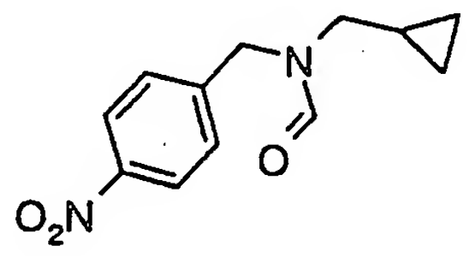
The starting material can be prepared for example as follows:

46 mmol 4-nitrobenzylbromide is added in portions to a solution of 185 mmol cyclopropylmethylamine in dichloromethane (temperature rises to about 30°C). The mixture is stirred overnight at room temperature, washed twice with water, dried over sodium sulfate

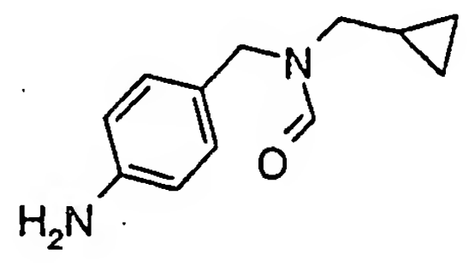
and evaporated and dried under a high vacuum to remove surplus amine. The raw product is converted to the hydrochloride by treatment with 5-6N hydrochloric acid in isopropanol with the addition of some ether. (4-Nitrobenzyl)cyclopropylmethylamine hydrochloride is obtained. Rf value 0.13 (ethyl acetate / petroleum ether 1:1).



A solution of 46 mmol (4-nitrobenzyl)cyclopropylmethylamine and 50.6 mmol Hünig's base in 50 ml dichloromethane is cooled to 10°C, and 46 mmol trichloroacetic aldehyde is slowly added. The mixture is stirred for 5 hours at 10–15°, the reaction mixture washed with 2N aqueous hydrochloric acid, the organic phase dried over sodium sulfate and evaporated in a vacuum, resulting in N-(4-nitrobenzyl)cyclopropylmethylamine. Rf value 0.33 (ethyl acetate / petroleum ether 1:1).

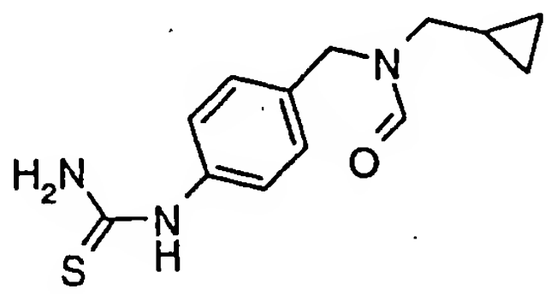


The raw product N-(4-nitrobenzyl)-N-cyclopropylmethylformamide is hydrogenated in the presence of 1.0 g palladium carbon (10%) in 200 ml tetrahydrofuran at room temperature and under normal pressure until saturation. Filtration via Hyflo Supergel (Fluka) yields a colourless solution of N-(4-aminobenzyl)-N-cyclopropylmethylformamide. This solution is used directly in the next step without further purification. Rf value 0.23 (ethyl acetate / petroleum ether 1:1).

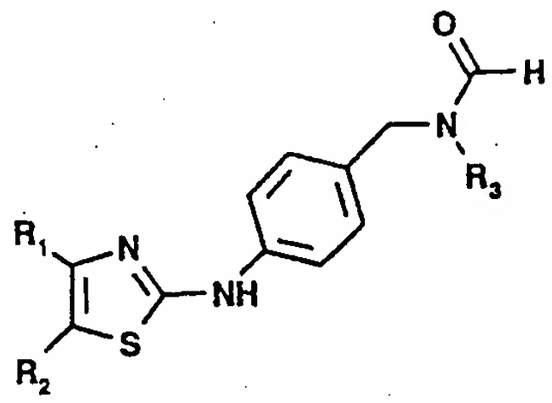


To the solution of N-(4-aminobenzyl)-N-cyclopropylmethylformamide obtained above, 46 mmol benzoylisothiocyanate is added drop by drop. The solution is stirred for 4 hours and concentrated by evaporation under a vacuum. The resulting intermediate product is

readily hydrolysed by treatment in a mixture of methanol and 46 mmol potassium carbonate in 100 ml water. After methanol has been evaporated off, the product is extracted with dichloromethane, dried and crystallized with ether, resulting in N-cyclopropylmethyl-N-(4-thioureabenzyl)formamide. Rf value 0.07 (ethyl acetate / petroleum ether 1:1).

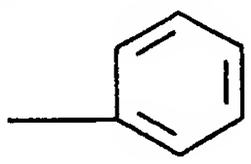
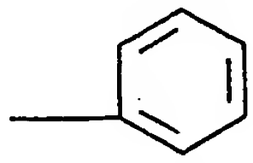
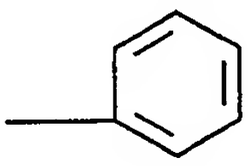
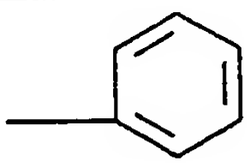
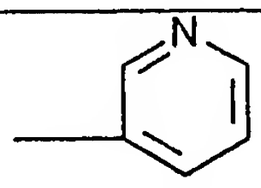
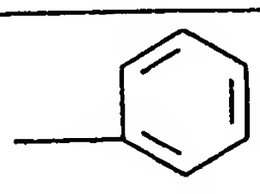


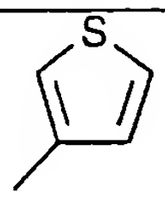
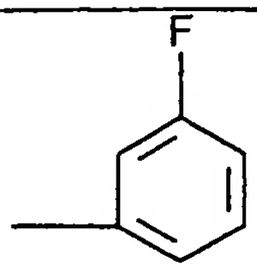
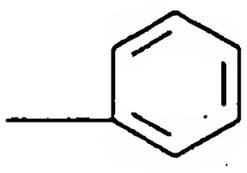
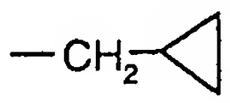
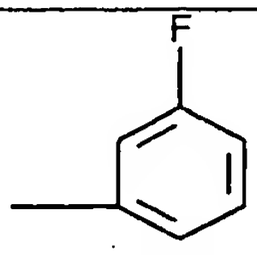
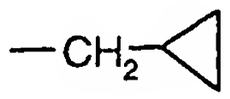
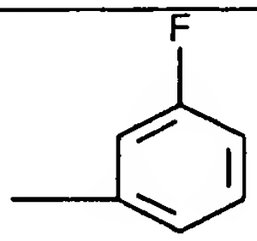
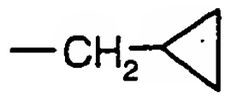
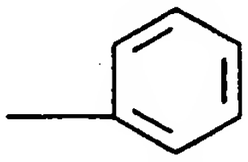
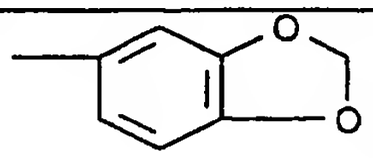
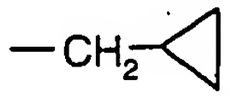
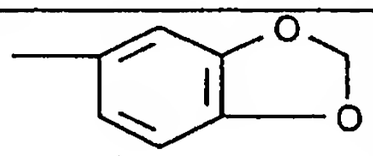
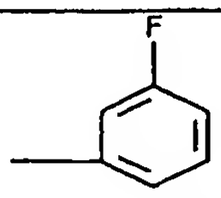
In analogous manner, for example as described in Examples 1, 18 or 19, the following compounds of formula



(I b)

can be prepared:

Example	R_1	R_2	R_3	Salt	m.p. [°C]
20		H	n-C_3H_7	HCl	158
21		H	i-C_3H_7	-	127
22		CH_3	C_2H_5	-	144
23		CH_3O	C_2H_5	HCl	148
24			i-C_3H_7	HCl	210

25		H	i-C_3H_7	HCl	182
26		H	$CH_3SO_2CH_2CH_2$	HCl	149
27		H		HCl	127
28		H		-	110
29		H		CH_3SO_3H	158
30		H	CF_3CH_2	HCl	173
31		H		HCL	195
32		H	CF_3CH_2	HCl	165
33		H	i-C_3H_7	-	139

The manufacture of the corresponding bromoketone starting material of the following examples is disclosed in

(22): Coppola, Gary M. et al.; Synlett (1995), Issue 11, 1143-4.

(23): McKay, William R.; Proctor, George R.; J. Chem. Soc., Perkin Trans. 1 (1981), Issue 9, 2435-42.

(24) Klose, Walter; Schwarz, Katica. J; Heterocycl. Chem. (1985), 22(3), 669-71.

Formulation example: hard gelatin capsules, comprising 100 mg active substance, for example N-isopropyl-N-[4-(4-phenylthiazol-2-ylamino)benzyl]formamide or a salt, for example the hydrochloride, thereof, can be prepared for example as follows:

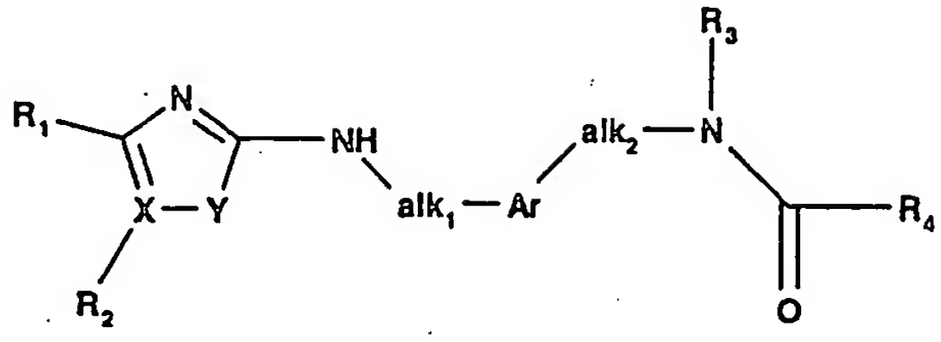
Composition (for 1000 capsules)

Active ingredient	100.0 g
Lactose	250.0 g
Microcrystalline cellulose	30.0 g
Sodium lauryl sulfate	2.0 g
Magnesium stearate	8.0 g

The sodium lauryl sulfate is added to the lyophilized active ingredient via a sieve with a mesh size of 0.2 mm. Both components are intimately mixed. Then first the lactose is added via a sieve with a mesh size of 0.6 mm and then the microcrystalline cellulose via a sieve with a mesh size of 0.9 mm. Thereupon these components are intimately mixed for a further 10 minutes. Finally the magnesium stearate is added via a sieve with a mesh size of 0.8 mm. After 3 minutes of further mixing, 390 mg each of the formulation obtained are filled into hard gelatin capsules of size 0.

What is claimed is

1. Compound of formula (I)



(I),

(i) alk_1 is a bond or C_1-C_4alkylene and alk_2 is C_1-C_4alkylene;
X is the C atom and Y the S, O or NH atom; or
X is the N atom and Y is the N atom;
Ar is phenylene;
R_1 is hydrogen, C_1-C_7alkyl, C_1-C_7alkoxy-C_1-C_7alkyl, C_3-C_8cycloalkyl-C_1-C_7alkyl, C_1-C_7alkoxy, C_1-C_7alkoxy-C_1-C_7alkoxy, CF_3, halogen, nitro or cyano, or R_1 is phenyl, pyridyl, pyrrolyl, furyl or thienyl;
R_2, has the same meanings as R_1 if X is C, or is hydrogen, C_1-C_7alkyl or C_3-C_8cycloalkyl-C_1-C_7alkyl if X is N;
R_3 and R_4 are independently hydrogen, C_1-C_7alkyl, C_1-C_7alkoxy-C_1-C_7alkyl, C_3-C_8cycloalkyl-C_1-C_7alkyl, halogeno-C_1-C_7alkyl, aminocarbonyl-C_1-C_7alkyl, wherein the amino group is unsubstituted or is monosubstituted or disubstituted independently by C_1-C_7alkyl or phenyl-C_1-C_7alkyl, or they are phenyl or phenyl-C_1-C_7alkyl; whereas R_3 and R_4 are not simultaneously hydrogen; or
R_3 and R_4 together are C_3-C_4alkylene;

wherein an (hetero)aromatic radical phenylene, phenyl, pyridyl, pyrrolyl, thienyl, furyl is independently unsubstituted or substituted once or several times by a substituent selected from the group consisting of C_1-C_7alkyl, C_1-C_7alkoxy-C_1-C_7alkyl, hydroxy, C_1-C_7alkoxy, C_1-C_7alkoxy-C_1-C_7alkoxy, CF_3, halogen, nitro and cyano;
(ii) also a corresponding compound of formula (I), wherein R_1 is phenyl disubstituted by oxy-C_1-C_2alkylene-oxy, which is furthermore unsubstituted or substituted once or several times by a substituent selected from the group consisting of C_1-C_7alkyl, C_1-C_7alkoxy-C_1-C_7alkyl, hydroxy, C_1-C_7alkoxy, C_1-C_7alkoxy-C_1-C_7alkoxy, CF_3, halogen, nitro and cyano;

(iii) also a corresponding compound of formula (I), wherein R_3 and R_4 are independently furanyl or pyranyl;
or a salt thereof.

2. A compound, according to claim 1, of formula (I), wherein
alk_1 is a bond or C_1-C_4alkylene and alk_2 is C_1-C_4alkylene;
X is the C atom and Y the S, O or NH atom; or
X is the N atom and Y is the N atom;
Ar is phenylene;
R_1 is phenyl or pyridyl;
R_2, has the same meanings as R_1 if X is C, or is hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl-C_1-C_4alkyl if X is N;
R_3 is C_1-C_4alkyl, C_1-C_4alkoxy-C_1-C_4alkyl, halogeno-C_1-C_4alkyl, aminocarbonyl-C_1-C_4alkyl, wherein the amino group is unsubstituted or is monosubstituted or disubstituted by C_1-C_4-alkyl or phenyl-C_1-C_4alkyl independently of one another, or it is phenyl-C_1-C_4alkyl;
R_4 is hydrogen or C_1-C_4alkyl; or
wherein an (hetero)aromatic radical phenylene, phenyl or pyridyl is independently unsubstituted or substituted once or several times by a substituent selected from the group consisting of C_1-C_4alkyl, C_1-C_4alkoxy, halogen, CF_3, cyano and nitro.
or a salt thereof.

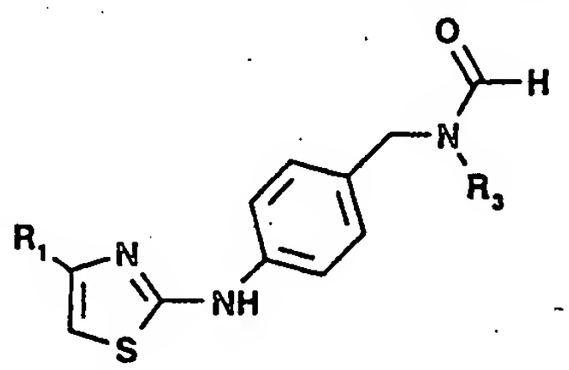
3. A compound, according to claim 1, of formula (I), wherein X is C ; Y is S; or a pharmaceutically acceptable salt, thereof.

4. A compound, according to claim 1, of formula (I),
wherein alk_1 is a bond;
alk_2 is C_1-C_2alkylene;
X is the C atom and Y is S;
Ar is phenylene;
R_1 is phenyl, phenyl disubstituted by oxy-methylene-oxy, pyridyl or thienyl;
R_2 is hydrogen, C_1-C_4alkyl, C_1-C_4alkoxy or phenyl;
R_3 is C_1-C_4alkyl, C_1-C_4alkoxy-C_1-C_4alkyl, C_3-C_6cycloalkyl-C_1-C_4alkyl, halogeno-C_1-C_4alkyl, aminocarbonyl-C_1-C_4alkyl, wherein the amino group is unsubstituted or independently monosubstituted or disubstituted by C_1-C_4alkyl, or it is furanyl-C_1-C_4alkyl;

R_4 is hydrogen;
wherein an (hetero)aromatic radical phenylene, phenyl, phenyl disubstituted by oxy-methylene-oxy, pyridyl, thienyl is independently unsubstituted or substituted once or more by a substituent selected from the group consisting of C_1-C_4alkyl, C_1-C_4alkoxy-C_1-C_4alkyl, hydroxy, C_1-C_4alkoxy, C_1-C_4alkoxy-C_1-C_4alkoxy, CF_3, halogen, nitro and cyano;
or a pharmaceutically acceptable salt thereof.

5. A compound, according to claim 1, of formula (I), wherein alk_1 is a bond; alk_2 is C_1-C_2-alkylene; X is the C atom and Y is S; Ar is 1,4-phenylene; R_1 is phenyl, phenyl substituted by halogen or phenyl disubstituted by oxy-methylene-oxy; R_2 is hydrogen; R_3 is C_1-C_4alkyl, C_1-C_4alkoxy-C_1-C_4alkyl, C_3-C_6cycloalkyl-C_1-C_4alkyl, or halogeno-C_1-C_4alkyl; R_4 is hydrogen; or a pharmaceutically acceptable salt thereof.

6. A compound, according to claim 1, of formula (I a),



(I a),

wherein
R_1 is phenyl, which is unsubstituted or substituted once or several times by a substituent selected from C_1-C_4alkyl and halogen;
R_3 is C_1-C_4alkyl, C_1-C_4alkoxy-C_1-C_4-alkyl, halogeno-C_1-C_4alkyl or C_1-C_4alkyl, which is substituted by C_1-C_4alkylaminocarbonyl; or a pharmaceutically acceptable salt thereof.

7. A compound, according to claim 6, of formula (I a), wherein
R_1 is phenyl or fluorophenyl; and R_3 is C_1-C_3alkyl; or a pharmaceutically acceptable salt thereof.

8. A compound, according to claim 6, of formula (I a), wherein
R_1 is fluorophenyl; and R_3 is C_3-C_6cycloalkyl-C_1-C_3alkyl; or a pharmaceutically acceptable salt thereof.

9. A compound, according to claim 1, selected from the group consisting of N-isopropyl-N-[4-(4-phenylthiazol-2-ylamino)benzyl]formamide, N-[4-(4-phenylthiazol-2-ylamino)benzyl]-N-(tetrahydrofuran-2-ylmethyl)formamide and N-cyclopropylmethyl-N-{4-[4-(3-fluorophenyl)thiazol-2-ylamino]benzyl}formamide or a pharmaceutically acceptable salt thereof.

10. A compound of claim 9 in the form of a hydrochloride.

11. A compound according to any one of claims 1 to 10 for use in the treatment of the human or animal body.

12. The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof according to any one of the claims 1–11 for the preparation of a medicament for the treatment of obesity and related diseases.

13. A pharmaceutical composition comprising a compound according to any one of the claims 1–11 and a pharmaceutically acceptable excipient or adjuvant.

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/EP 99/03682

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D277/42 C07D277/54 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 20821 A (NOVARTIS AG ;RUEEGER HEINRICH (CH); SCHMIDLIN TIBUR (CH); RIGOLL) 12 June 1997 (1997-06-12) abstract; claim 9 ---	1-13
A	WO 94 17035 A (THOMAE GMBH DR K) 4 August 1994 (1994-08-04) abstract; claim 1 ---	1-13
A	EP 0 787 727 A (SS PHARMACEUTICAL CO) 6 August 1997 (1997-08-06) abstract ---	1-13
A,P	EP 0 887 346 A (HOFFMANN LA ROCHE) 30 December 1998 (1998-12-30) abstract; claim 1 ---	1-13

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 September 1999	08/10/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Frelon, D

INTERNATIONAL SEARCH REPORT

Int[illegible]tional Application No
PCT/EP 99/03682

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 98 32753 A (MATHVINK ROBERT J ;PARMEE EMMA R (US); TOLMAN SAMUEL (US); WEBER A) 30 July 1998 (1998-07-30) abstract; claim 1	1-13

INTERNATIONAL SEARCH REPORT

ɔrnational application No.
PCT/EP 99/03682

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1 and 2 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a relatively small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds prepared in the examples and closely related homologous thereof, that is, compounds wherein R1 is a ring, Ar represents a 1,4-phenylenyl and R3+R4 do not form a ring.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

information on patent family members

Int[illegible]tional Application No
PCT/EP 99/03682

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9720821 A	12-06-1997	AU 7692696 A	27-06-1997
WO 9417035 A	04-08-1994	DE 4301452 A	21-07-1994
		DE 4326465 A	09-02-1995
		AU 683442 B	13-11-1997
		AU 5884194 A	15-08-1994
		CA 2153582 A	04-08-1994
		CZ 9501878 A	17-04-1995
		EP 0680469 A	08-11-1995
		FI 953467 A	18-07-1995
		HU 73770 A	30-09-1996
		JP 8505862 T	25-06-1996
		NO 952869 A	19-09-1995
		NZ 259872 A	27-07-1997
		US 5616620 A	01-04-1997
		US 5807875 A	15-09-1998
		ZA 9400368 A	19-07-1995
EP 0787727 A	06-08-1997	CA 2196400 A	01-08-1997
		CN 1167764 A	17-12-1997
		JP 9268189 A	14-10-1997
		US 5710152 A	20-01-1998
EP 0887346 A	30-12-1998	AU 7310298 A	24-12-1998
		BR 9802201 A	25-05-1999
		CA 2240136 A	23-12-1998
		CN 1203228 A	30-12-1998
		CZ 9801974 A	13-01-1999
		HR 980353 A	30-04-1999
		JP 11071353 A	16-03-1999
		NO 982884 A	28-12-1998
		PL 326959 A	04-01-1999
WO 9832753 A	30-07-1998	AU 6038498 A	18-08-1998
		HR 980044 A	31-10-1998
		ZA 9800647 A	28-07-1998